REMARKS

Entry of the foregoing and favorable reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claims 27 and 28 have been added. Support for new Claim 27 appears at least on page 3 of the specification as filed. Applicants submit that no new matter has been added via this amendment.

Claims 1 to 8, 25 and 26 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Haicheur et al. (J. Immunologu 2000, 165:3301-3308) in view of Wang et al WO 95/11998) and Eichner (U.S. Patent 5,944,311). For the following reasons, this rejection is respectfully traversed.

Haicheur et al. discloses that the nontoxic B subunit of Shiga toxin can be used as a vector to deliver a tumor peptide derived from the mouse mastocytoma p815A and can induce CTL in mice without the use of an adjuvant. In this regard, the tumor Ag P815A was fused to the Shiga B toxin subunit using recombinant technology. The peptides, which were fused to the B subunit of Shiga toxin were synthetic peptides SIINFEKL, encompassing the 257-264 residues of OVA and LPYLGWLVF, encompassing the 35-43 residues of P1A. Thus the peptides which were **fused** to the B subunit of Shiga toxin were eight and nine amino acids in length, respectively.

Haicheur et al. also disclose that these fusion proteins elicit CTL and target dendritic cells to allow MHC Class I-restricted pathway presentation. This reference fails to disclose or suggest using a cysteine residue coupled to the C-terminus of the Shiga toxin B subunit. Furthermore, this reference fails to disclose or even suggest that proteins can be coupled to this universal carrier by covalently linking an S- residue by a –S-S-, or S-CO-, or S-CH_2 or S-NH linkage and the universal carrier maintains its Gb3 receptor function and retrograde routing capacity.

WO 95/11998 discloses structured synthetic antigen libraries composed of related peptides synthesized simultaneously in a single peptide sequence. This sequence is chosen based on a mathematical formula AA1 to AAii representing the amino acid sequence from N- to C-terminus of the library, j varies from 1 to n where n represents the number of possible amino acids known at the ith amino acid position.

The SSAL is from about 8 to about 100 amino acids in length depending on the particular site. WO 95/11998 discloses that three lysines can be added at the amino terminus to increase peptide solubility, cysteine can be added to facilitate directed coupling to carrier molecules and methionine can be added for cyanogen bromide cleavage. The carrier molecules include BSA, human serum albumin red blood cells or latex particles.

WO 95/11998 does not disclose that the amino acid situated next to the csyteine group is an amino acid devoid of a sulfhydryl group. Nor does this patent disclose that a molecule can be attached which is a cytotoxic drug or a pro-drug to be targeted to tumor cells expressing Gb3 receptors.

Furthermore, there is no specific targeting to Gb3 receptor expressing cells in WO 95/11998. Thus, a C-terminal cysteine would have no possible effects on the targeting.

U.S. Patent 5,994,311 discloses cell adhesion peptides for modifying the adhesion capacity of eukaryotic molecules between each other and to promote or inhibit the cell/cell adhesion of eukaryotic cells. More specifically this patent describes adhesion peptides having at least the amino acid sequence of:
Aa3-Aa2-Aa1-$(AaX)_n$-$(AaY)_m$ wherein n is either 0 or 1, m is either 0 or 1 when n=1 and Aa1 indicates the terminal amino acid at the carboxy terminal end of the peptide when n=m=0, and wherein AaX and AaY are any optional amino acid in each case, Aa1 is Gly, Pro or Asp, Aa2 is Asp, Leu, Asn or Ser and Aa3 is Leu, Ile, Phe or Gly.

The Examples show particular peptides that have a cysteine in the near terminal in order to couple the peptide to other carrier molecules. However, there is only one sole cysteine in all of the peptides described therein at the C-terminal.

The combination of references fails to render the present invention obvious since it was not predictable whether two cysteines in the Shiga B toxin vector would in fact lead to the targeting of the Gb3 receptor expressing cells. One can see from the amino acid sequence of the universal carrier, set forth on page 3 of the specification, that there are two cysteine residues in the sequence. These cysteine residues are separated by a multitude of amino acids and thus have the possibility to form disulfide bridges. It was very unexpected by the inventors of the present invention that the addition of an additional cysteine moiety did not cause internal disulfide bridges thus preventing the binding to the Gb3 receptor to occur and/or failure to enter the correct retrograde routing path in the cell due to aggregation and clustering of the universal carrier.

Thus, even though the Examiner deems that it was well known in the art to add a cysteine residue as a linker, it was not evident that this additional cysteine residue would not alter the structure of the Shiga toxin B subunit in such a way that its carrier properties would be greatly affected. Applicants submit that this is an unexpected property that by adding an additional

cysteine residue that targeting to the GB3 receptor cells was not modified. This is not taught or even suggested in the prior art.

Therefore in view of the above, withdrawal of this rejection is respectfully requested.

Claims 1 to 8, 25 and 26 have been rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. For the following reasons, however, this rejection is respectfully traversed.

In rendering this rejection the Examiner deems that a "functional equivalent thereof" lacks written description. Applicants submit that at least the paragraph bridging pages 2 and 3 discusses the functional equivalent as meaning "a polypeptidic sequence having the capacity to bind specifically to the Gb3 receptor and/or to trigger an internalization of an antigen and its presentation in an MHC class-I restricted pathway, or both MHC class I and class II on the same antigen presenting cells."

Furthermore, Shiga-like toxins were also well known to the skilled artisan at the time of filing of the present invention as taught in Reference 8, a copy of which is enclosed for the Examiner as Annex 1. This reference describes that toxins produced by other microorganisms other than *S. dysenteriae* type 1 are called Shiga-like toxins since that can be neutralized with antibodies against Shiga toxin. Moreover, the biological and biochemical properties of *E. coli* purified Shiga toxin and SLT-1 are identical.

Therefore, Applicants submit that there is written description for functional equivalents and the skilled artisan would from the written description in the specification coupled with the general knowledge in this art would know that the inventors had possession of the presently claimed invention and the functional equivalents.

Therefore in view of the above, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D., Reg. No. 40,069 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____

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